shown not to be applicable. Such groups might exist among the socially disaffiliated and those without a regular source of health care, possibly including some alcoholics, drug addicts, and migrants. Groups such as health workers who may be at particular risk of exposure to unrecognized pulmonary tuberculosis should, where possible, be kept under surveillance for evidence of newly acquired tuberculous infection. It must be recognized that only the occurrence of new infections reflects whether transmission is actually occurring.

In other areas of the world, particularly in those countries in which there is greater transmission of tuberculous infection within the population, BCG vaccination is practiced on a much wide scale. In highly endemic countries, vaccination of all newborn infants is recommended.

Unquestionably, BCG vaccine plays a major role in the control of tuberculosis in many countries of the world. In a country such as the United States, in which transmission of tuberculosis is at a low level, BCG vaccine may properly be viewed as an adjunct to tuberculosis control, supplementing methods of case detection, chemotherapy, and preventive treatment in those limited segments of the population in which an excessive rate of new infections can be demonstrated and the usual surveillance and treatment programs have failed or cannot be readily applied. Tuberculin-negative persons unavoidably exposed in other parts of the world to populations in which there is significant tuberculosis transmission might also benefit from BCG vaccine.

Since BCG is a live mycobacterial vaccine, it should not be given to persons with impaired immune response, particularly impaired cell-mediated immune mechanisms, such as occurs with certain congenital immunodeficiency states, lymphoreticular malignancies, sarcoidosis, or when immunologic response has been suppressed with corticosteroids, alkylating agents, antimetabolites, or radiation.

Although no harmful effects of BCG on the fetus have been observed, it is probably prudent to avoid vaccination during pregnancy unless there is an excessive risk of unavoidable exposure to infective tuberculosis.

Safety of BCG Vaccine

The early history of BCG vaccination was tranished in 1930 by the Lübeck, Germany catastrophe, in which 72 of 251 infants died of tuberculosis following BCG vaccination. That disastrous episode was subsequently shown to be due to contamination of the vaccine by a strain of virulent tubercel bacilli. Excluding, Therefore, that episode, the safety of BCG vaccine has never been seriously contested. Progressive disease has occasionally been reported in immunosuppressed hosts, particularly in hosts with defects of cell-mediated immune mechanisms. In a summary of the world's literature through 1968, only 13 fatalities were cited as due to BCG vaccination (excluding the 72 fatalities noted above).

Efficacy of BCG Vaccination in Man

Table I presents, in summary form, the results of eight controlled trails of BCG vaccination against tuberculosis. A strikingly wide range of efficacy is seen, ranging from 0 to 80 percent. Three trials, those in Georgia (1947), in Georgia-Alabama (1950), and in Illinois (1947), showed no or very litte effect. The Puerto Rico trial (1958) and the South India trial (1968) showed mild to moderate degrees of protection. Finally, the trial in North American Indians (1953), Chicago infants (1961), and the Medical Research Council trial in Great Britain (1972) showed excellent protection.

These trials vary in composition of study groups, age at vaccination, methods of vaccine administration and dosage, and origin of vaccine strains.

TABLE 1—RESULTS OF EIGHT CONTROLLED TRIALS OF BCG VACCINATION AGAINST TUBERCULOSIS [1]

Population group and reference	Period of intake and age range	Criterion of eligibility for vaccination	Source of vaccine	Duration of followup (years)	Vaccination group	Number of subjects	Cases of tuberculosis		Protective efficacy (percent)
							No.	Rate [2]	
	1935–1938				Unvaccinated	1,457	238	1,563	
North American Indians (8 tribes) (Stein & Aronson (Ref. 2)).	0–20 years	Negative to 0.005mg PPD—Seibert (250 TU).	Henry Phipps Institute, Philadelphia.	9–11					80 [3]
					BCG	1,551	64	320	
					Unvaccinated	1,665	65	[4] 223	
	1937–1948								
Chicago infants, high-risk areas (Rosenthal (Ref. 3)).	Under 3 months	No initial tuberculin testing.	Tice Lab., Chicago [4].	12–23					75
					BCG	1,716	17	[4] 57	
					Unvaccinated	2,341	3	11	
	1947								
Georgia, school children (Comstock & Webster, (Ref. 5)).	0–6–17 years	Under 5 mm to 0.002 mg RT 18 (100 TU).	Tice Lab., Chicago [4].	20					None
					BCG	2,498	5	17	
					Unvaccinated	404	8		
	1947–1948								
Illinois, school for mentally retarded (Bettag (Ref. 6)).	Adolescents and young adults.	Negative in 1/1000 and 1/100 OT.	Tice Lab., Chicago [4].	12					None
					BCG	531	12		
					Unvaccinated	27,338	73	43	
	1949–1951								
Puerto Rico, general population (Palmer (Ref. 7)).	1–18 years	Under 6 mm to 0.0002 mg RT 19–20–21 (10 TU).	State Dept. of Health, NY.	5½–7½					31
				(means: 6.3)	BCG	50,634	93	30	
					Unvaccinated	17,854	32	13	
	1950								
Georgia, Alabama, general population (Comstock & Palmer, (Ref. 8)).	5 years and over	Under 5 mm to 0.0001 mg RT 19–20–21.	Tice Lab., Chicago [4].	14					14
					BCG	16,913	26	11	
					Unvaccinated	12,699	240	128	
	1950–1952								
Great Britain, urban population (British Medical Research Council (Ref. 9)).	14–15½ years	Under 5 mm to 0.1 ml 1-100 Old Tuberculin (100 TU).	Statens Serum-Institute Copenhagen.	15					78
					BCG	13,598	56	28	

TABLE 1—RESULTS OF EIGHT CONTROLLED TRIALS OF BCG VACCINATION AGAINST TUBERCULOSIS [1]—Continued

Population group and reference	Period of intake and age range	Criterion of eligibility for vaccination	Source of vaccine	Duration of followup (years)	Vaccination group	Number of subjects	Cases of tuberculosis		Protective efficacy (percent)
							No.	Rate [2]	
South India, rural population Frimondt-Moller (Ref. 10)).	1950–1955 All ages	Under 5 mm to 5 TU RT 19–20–21.	BCG Lab., Madras	9–14	Unvaccinated	5,808	46	89	52
					(mean: 12.3) BCG	5,069	28		61

[1] Adapted from: British Medical Research Council (1972) Bulletin of the World Health Organizations, 46:381.
[2] Annual rate per 100,000 population, usually allowing for losses from observations.
[3] The protective efficacy against death from tuberculosis was 82 percent for a period of 18–20 years (Aronson (Ref. 4)).
[4] This laboratory has issued a number of strains at different times and it is not known whether the strains used in these three trials were the same or not.
[5] Assuming a mean observation period of 17.5 years.

Methods of case detection have been particularly variable, and become critically important in those trials in which the detected incidence of tuberculosis in the control group was already quite low. For example, the British Medical Research Council trials used intensive followup with chest films, whereas most American trials relied primarily on reports from health departments.

How can such widely disparate results be explained, if at all? Among suggestions that have been put forward are that the differences stem from nutritional or from genetic differences between the populations involved. The nutritional differences do not tally particularly well with the variations found in efficacy, and there is insufficient information available to assess whether genetic differences might be responsible. Three other possibilities merit serious attention.

First is the explanation for the poor results found in the Georgia-Alabama trials by Palmer (Ref. 7) and his colleagues. Palmer suggested that in areas where nonspecific tuberculin sensitivity was common, as is true throughout much of the Southeastern United States, a large proportion of the population had already acquired some natural immunity against virulent tuberculous infection from a typical mycobacterial infections. In this situation, vaccination with BCG would only supplement the immunity that already existed and would not make as large an apparent contribution as in an area that was relatively free from atypical mycobacterial infections. This hypothesis has been experimentally supported in guinea pigs, showing that infection with other mycobacteria did indeed confer protection against subsequent virulent challenge. This protection, however, was always less than was conferred by BCG. Palmer suggested that this explanation could, at least in part, reconcile the widely differing findings of the Medical Research Council trial in Great Britain and that in the Southeastern United States.

Hart (Ref. 11), however, subsequently showed that while differences in the frequency of other mycobacterial infections could well have contributed to this difference, it would scarcely be the whole story. Hart calculated that if none of the subjects in the Georgia-Alabama trial had any natural protection from other mycobacterial infections, the apparent efficacy of the vaccine in that population would have risen from the actual 14 percent to only 25 percent. Hart postulated that some other influence must be operating, and suggested as an inescapable conclusion that the vaccine used in the Georgia-Alabama trial must have been less potent than the Danish strain used in the Medical Research Council trial.

This is, then, the second possibility that merits attention; namely, that different products all labeled as BCG may differ widely in their immunizing effect, and that this could be the main reason, or even the only one, for the mutually contradictory results of different BCG trials. The manufacturer of the vaccine used in the Georgia-Alabama trial has also claimed that vaccine was administered by inappropriate technique.

At this date, it is difficult if not impossible to ascertain whether the vaccines or the technique of administration or both were responsible for the divergent results noted in controlled field trials. There is independent evidence, however, that BCG strains used in vaccine production by the laboratory supplying vaccine for two of the field trials that showed no protection were very weak in terms of multiplication, allergenic potency, and protection in animals.

The third possibility is one recently suggested by Sutherland (Ref. 12). Sutherland has observed that areas with a high incidence of tuberculosis in the unvaccinated group showed a high efficacy of BCG vaccine, whereas those with a low incidence of tuberculosis in the unvaccinated group showed a low efficacy, suggesting that the efficacy of BCG may be greater in an area where there is much tuberculosis than in an area where there is only little. If this relationship is genuine, it suggests that superinfection of vaccinated subjects with virulent tubercle bacilli or other mycobacteria may be necessary to maintain the protection conferred by BCG vaccine. This concept is not without its parallels in other infectious diseases, but has not heretofore been suggested for tuberculosis and BCG vaccine. A review of the eight trials noted above demonstrates an association between the degree of protection and the degree of challenge.

All of the controlled field trials cited previously were carried out using liquid BCG vaccines. There have thus far been no field trials of freeze-dried BCG vaccines reported, though one is currently in progress in India. To date the only evidence supporting the efficacy in man of freeze-dried BCG vaccine is extrapolated from uncontrolled experience. The results suggest, but do not prove, that the freeze-dried vaccine prepared by Glaxo Laboratories is as effective in man as the liquid Copenhagen vaccine used in the Medical Research Council trial in Great Britain.

On the basis of presently available information, judgments concerning the safety and efficacy of BCG vaccines licensed for use in the United States must be made by inference from historical data plus whatever inference can be drawn from tuberculin conversion in man.

Special Problems

Marked differences in the immunogenic and sensitizing potency of BCG strains were demonstrated over 20 years ago. During continuous serial subculturing (the traditional way of maintaining strains prior to the introduction of seed lot systems), the emergence of mutant strains was unavoidable. Mutants that have a faster growth rate in vitro than do the parent cells can, in a relatively short period of time, emerge as the dominant strain.

There have been striking spontaneous changes in such attributes as morphology, pigmentation, rate of growth, and even in the ability to protect animals against experimental infection. In the case of such marked phenotypic change, the "daughter" strain can no longer be regarded as the same as the parent strain. Seed lot systems have been used to preserve BCG strains for little more than a decade. Thus, there is no single scientifically defined entity known as BCG vaccine; there are rather many different BCG vaccines, with varied biological characteristics and almost surely varied immunizing potency in man. Such a state of affairs is, to say the least, highly undesirable.

Evidence concerning the relative merits of various established BCG strains is indirect and derived largely from animal studies that are sometimes mutually contradictory. There is no doubt that strains differ widely in terms of virulence and also in terms of protective efficacy in certain animal models.

The need for further strengthening of animal model systems was highlighted by the recent report of Wiegeshaus (Ref. 13) and associates. In order to determine if the method by which a vaccine was tested was a major factor contributing to the results, an experiment was conducted in which a series of five different vaccines was distributed to each of nine participating laboratories. Each investigator evaluated the potency of the vaccines in one or more animal models of his own choosing. This, in effect, held the method of vaccine preparation constant, while permitting all other variables to change. The ranking of the five vaccines was essentially random, thus demonstrating that the method by which the vaccine is tested in animals markedly influences its apparent potency.

Nevertheless, many authorities consider that there is some correlation between the potency of vaccine for animals and its protective potency for man. BCG vaccine with a high potency in animals may be expected to induce strong and long-lasting protection against turberculosis in man, whereas a vaccine with low potency for animals may be virtually worthless for vaccination of humans. Thus, it would seem reasonable to choose for the production of vaccine only strains that are metabolically fully active, have good immunogenic potency in animals, and induce strong and lasting tuberculin sensitivity in humans.

One further controlled field trial of BCG vaccine is currently in progress in India, supported by the World Health Organization and the United States Public Health Service. This is the only controlled field trial of freeze-dried vaccines and has utilized vaccines from two production laboratories at two dosage levels. This may well be the last opportunity to carry out well-controlled field trials of tuberculosis immunoprophylaxis, and the results will be awaited with considerable interest.

Recommendations

Public support should be made available for further development and evaluation of BCG vaccines in animal model systems in order to provide models that are known to reflect protective efficacy in man accurately.

The results of the field trail currently in progress in India should be reviewed, when available, with particular attention to the adequacy of the scientific basis on which to recommend that all BCG vaccines distributed in the United States be prepared from the same seed lot strain of demonstrated efficacy in man.

Basis for Classification

The Panel considers that there is reasonable evidence of safety and efficacy of the three licensed BCG vaccines and therefore recommends that they be classified in Category I. This recommendation is not based on unassailable evidence of the safety and efficacy of these individual products, but rather on the general totality of experience reported in previous field trials of BCG vaccines. The Panel arrived at its decision more by a consideration of the alternatives than by clear conviction that a Category I classification was fully deserved.

There is no evidence on which to classify these products as Category II unsafe and/or ineffective; although a classification in Category III was seriously considered. Given the lack of an animal model system directly correlated with efficacy in humans, such a classification would place an impossible demand on manufacturers to carry out controlled field trials of their BCG vaccines.

Therefore, the Panel recommends that these products be placed in Category I, with the added stipulation that these products be reviewed again when the current World Health Organization-United States Public Health Service field trail in India is completed. If there emerges compelling evidence of efficacy of one or another BCG strain in that trial, subsequent review might well mandate U.S. licensed manufacturers to use that strain for vaccine production.

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Specific Product Reviews

BCG Vaccine Manufactured by Connaught Laboratories Limited

1. *Description.* This is a freeze-dried vaccine prepared from a strain of living attenuated bovine tubercle bacilli. The reconstituted vaccine for intracutaneous use is adjusted to contain between 10×10^6 and 30×10^6 viable cells per mL. Extensive details are provided of the manufacturing process itself. The origin of the Connaught Laboratories' BCG seed lot is presented in detail, and summarized as follows: Dr. Armand Frappier of the Institute of Microbiology and Hygiene of the University of Montreal received the strain on July 11, 1937, from Dr. Guerin of the Institute of Pasteur in Paris. It was apparently maintained in cycles of alternating 14-day passage on bile-potato medium followed by glycerimated-potato medium, followed again by bile-potato medium. A subculture was sent to Connaught Laboratories in April 1948 and the culture was thereafter maintained in cycles consisting of five consecutive biweekly passages on glycerinated-water-potato medium, followed by one passage on glycerinated-bile-potato medium for 2 weeks. The strain was lyophilized in 1967, when a seed lot system was introduced.

2. *Labeling*—a. *Recommended use/indications.* Under "selection of persons" in the package insert, the vaccine is stated to be given only to tuberculin negative individuals. It is recommended for use in the following groups of individuals.

All tuberculin negative individuals:

(1) Who by occupation are exposed to tuberculosis such as nurses, medical students, and hospital attendants.

(2) Who are in the population groups or areas with high tuberculosis morbidity and mortality rates.

(3) With a known exposure to tuberculosis, or where an exposure may occur, as in the household contacts of patients with tuberculosis admitted to or discharged from hospitals or sanitoria.

b. *Contraindications.* It is said to be inadvisable to vaccinate individuals suffering from "general malaise" although that entity is not further defined, or intercurrent acute infections such as measles, whooping cough, eczema, or furunculosis. Caution is expressed that BCG vaccines should not be given with other antigens, and that there be sufficient time for reactions to either BCG vaccine or to other antigens to subside before vaccination is carried out with the other.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* In experiments carried out in 1963 to 1965 (Ref. 1), when Connaught Laboratories was initially working with lots of freeze-dried vaccine, series of protection tests were carried out in both mice and guinea pigs using three vaccines, Glaxo Laboratories' freeze-dried BCG vaccine, Connaught Laboratories' freeze-dried BCG vaccine, and a Japanese freeze-dried BCG vaccine. In both mice and guinea pig experiments, the Glaxo Laboratories' and Connaught Laboratories' products showed clear-cut evidence of protective efficacy in both mice and guinea pigs, whereas the Japanese freeze-dried product produced no protection at all in mice, and was substantially less effective than the Glaxo Laboratories' or Connaught Laboratories' products in guinea pigs.

The product meets Federal requirements. Current animal efficacy tests on lots of vaccine are apparently limited to a guinea pig potency assay, measuring only tuberculin skin test conversion.

(2) *Human.* No controlled studies of the efficacy of Connaught Laboratories' freeze-dried BCG vaccine have been conducted. There are several older studies in the Canadian literature showing the efficacy of a liquid vaccine prepared by Dr. Frappier, both in nurses and in new-borns, but these data were not cited in the Connaught Laboratories' submission. Several studies of conversion rates have been carried out with the Connaught Laboratories' freeze-dried product, indicating that the Connaught Laboratories' product is comparable to other freeze-dried products in respect to producing very high skin test conversion rates.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The general body of world literature relating to the safety of BCG vaccine is cited in the submission to the Panel (Ref. 2) as evidence of safety of the Connaught Laboratories' freeze-dried product. The submission notes a few cases of postvaccination abscesses and ulceration following Connaught Laboratories' BCG, but in each case these cleared up quickly and there was no evidence of tuberculosis.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product is satisfactory.

4. *Critique.* This is generally a thorough and complete submission from Connaught Laboratories. The information supplied by the manufacturer, the tests that this product is required to pass, and the general body of data concerning the safety and efficacy of BCG vaccines in humans are sufficient to place this product in Category I, in accordance with the discussion of this issue in the generic statement. The labeling is clear, but should be revised to reflect the current recommendations of the Public Health Service Advisory Committee on Immunization Practices.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

BCG Vaccine Manufactured By Glaxo Laboratories, Ltd.

1. *Description.* This is a freeze-dried BCG vaccine, being a suspension of a living culture of a strain of the bacillus of Calmette and Guerin. It is prepared from a Glaxo Laboratories' substrain of the Copenhagen strain of BCG, dispersed in Sauton's medium with Triton, and cultured for 14 days at 37 °C. The concentration is adjusted so that viability counts falls between 4 x 10G56 to 9×10^6 viable particles per mL for a low potency vaccine and 8×10^6 to 25×10^6 for a high potency vaccine for intradermal injection. Five $\times 10^7$ to 25×10^7 viable particles per mL of vaccine are used when the vaccine is intended for percutaneous administration.

2. *Labeling*—a. *Recommended use/indications.* The labeling is essentially a verbatim statement of the 1966 Public Health Service's Center for Disease Control statement of the special panel of public health and tuberculosis specialists. This states, in effect, that BCG vaccine should be used only for the uninfected individual or small groups of uninfected individuals living in unavoidable contact with one or more controlled infectious persons who cannot or will not obtain or accept supervised treatment.

b. *Contraindications.* BCG vaccine is contraindicated in tuberculin-positive individuals. In addition, it should not be given to patients who are immunosuppressed, whether as a result of underlying disease or treatment.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* There is general agreement that there is

no animal test of potency of BCG vaccine known to correlate directly with protective efficacy in man. This is so stated in the Glaxo Laboratories' submission.

2. *Human.* Several published works are cited in the submission to the Panel (Ref. 3) indicating the high skin test conversion rate when Glaxo Laboratories' freeze-dried BCG vaccine was used as directed. Additionally, the study of Springett and Sutherland (Ref. 4) is cited in which the efficacy of Glaxo Laboratories' freeze-dried BCG vaccine is retrospectively compared to the earlier experience in Birmingham when Copenhagen BCG vaccine in liquid form was used. In their analysis, the Glaxo Laboratories' freeze-dried vaccine performed just about as well as did the liquid Copenhagen vaccine. The authors point out that this was not really a controlled randomized trial, but rather a retrospective analysis using estimates of tuberculous experience in unvaccinated subjects. This is the only evidence, and indirect evidence at that, of effectiveness of any freeze-dried BCG vaccine.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The work of the British BCG Control Center is reported in its entirety (Ref. 3), and provides substantial evidence of the safety of Glaxo Laboratories' freeze-dried BCG vaccine.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product appears satisfactory.

4. *Critique.* This submission appears quite adequate. This information supplied by the manufacturer, the tests that the product is required to pass, and the general body of data regarding the safety and efficacy of BCG vaccine in humans are sufficient to place this product in Category I. The strain history is clarified, the Glaxo Laboratories' substrain being obtained from the Staten Seruminstitut in Copenhagen during the course of the Medical Research Council trial and immediately lyophilized. This culture has served as the master seed lot for vaccine production at Glaxo Laboratories since freeze-drying vaccine was marketed in 1957. The only remaining issue is whether the vaccine has retained full immunizing potency after freeze-dried and storage. The Panel believes that the retention of potency under these conditions is quite likely. (See discussion of this issue in the Generic Statement.)

There is no direct evidence that percutaneous vaccine is equal in protective efficacy to intradermal vaccine. One study (Ref. 5) is cited showing good comparability of tuberculin conversion rates when both routes were evaluated concurrently. In some recent studies, however, vaccine given by percutaneous multiple puncture methods has been less effective, as measured by skin test conversion, than vaccine given intradermally.

The labeling should be updated to reflect the current recommendations adopted by the Public Health Service Advisory Committee on Immunization Practices. Additionally, it would be of help to mention the size of needle to be used in intradermal injection.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

BCG Vaccine Manufactured by University of Illinois

1. *Description.* The BCG vaccine is a freeze-dried preparation of a culture of the Calmette and Guerin strain of *Mycobacterium bovis*, prepared from a substrain of the Pasteur Institute strain and freeze dried in lactose buffered salt solution. When reconstituted it contains 1×10^8 to 8×10^8 colony forming units per mL. A memorandum on the origin of the BCG strain used in the vaccine is included in the revised data submission from the manufacturer.

2. *Labeling*—a. *Recommended use/indications.* A package insert as such was not provided, but there is a 12 to 15 page document in the revised submission that appears to be a package insert. The vaccine is recommended as indicated for tuberculin-negative persons who are exposed to risks of tuberculosis infection. No mention is made of medical or paramedical personnel, but some emphasis is placed on the desirability of BCG vaccine for children who live in, or plan to travel in, areas where tuberculosis is prevalent, or are in situations where there is likelihood of exposure to adults with active or recently arrested pulmonary or renal tuberclulosis.

b. *Contraindications.* The vaccine is contraindicated in persons with a strong tuberculin reaction, fresh smallpox vaccination, or in burns. Severe immunodeficiency states, whether congenital, disease produced, or drug induced, are also listed as a contraindication.

3. *Analysis*—a. *Efficiacy*—(1) *Aninal.* There is an extensive review of animal data in the submission to the Panel (Ref. 6), particularly in mice and guinea pigs, showing the protective efficacy of BCG vaccine in the animal systems, including data as recently as 1966 to 1970, relating to the current Tice product. It should be noted, however, that the efficacy of BCG vaccine in animal systems is not well-correlated with efficacy in humans.

(2) *Human.* The submission to the panel (Ref. 7) provides an extensive review of both the controlled and uncontrolled studies carried out in the Chicago area from 1937 through the early 1950's. Some of this material has already been published. In the report by Rosenthal in 1961 (Ref. 8), there was good evidence that the vaccine was effective in reducing the rate of tuberculosis in children who had been vaccinated by a multiple puncture method at birth. Both liquid an freeze-dried vaccines were used.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Over the past 35 years, many thousands of vaccinations were performed using Tice vaccine, No fatalities have been directly attributable to BCG vaccine in the controlled field trials in Chicago. This is acceptable evidence of safety of this vaccine. In addition, the world literature attesting to the safety of BCG vaccine, as summarized by Mande, is noted (Ref. 9). From 1931 to 1968, 13 fatalities have been reported as due to BCG vaccine, with probably over 500 million doses of BCG vaccine having been given.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product appears to be satisfactory.

4. *Critique.* The 1961 Rosenthal study (Ref. 8) is sometimes criticized as not being completely double-blinded, but overall it may be accepted as substantial evidence of efficacy of the vaccine. Studies carried out since that time have not been as well or at all controlled. There is, however, no mention in the submission of the several field trails using Tice vaccine that showed minimal or no protection. These include the Muscogee County Georgia study, the Georgia-Alabama study, and the Bettag study in an Illinois State school.

Nevertheless, information supplied by the manufacturer, the tests that this product is required to pass, and the general body of data relative to the safety and efficacy of BCG vaccines in man are considered sufficient to place this product in Category I, in accordance with the discussion of this issue in the Generic Statement. The labeling should be revised to include the current recommendation of the Public Health Service Advisory Committee on Immunization Practices.

5. *Recommendations.* With the exception of one Panel member who recommended that this product be